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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,948	01/09/2006	Shigeyuki Yokoyama	P/2850-106	2037

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OSTROLENK FABER GERB & SOFFEN
1180 AVENUE OF THE AMERICAS
NEW YORK, NY 100368403

EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,948	YOKOYAMA ET AL.	
	Examiner	Art Unit	
	Kagnew H. Gebreyesus	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *8-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/27/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/05 & 12/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Acknowledgment for priority is made to this application which is a 35 U.S.C. § 371 national phase conversion of PCT/JP2003/014028 filed 31 October 2003, which claims priority to Japanese Application No. 2002-318846 filed on 31 October 2002.

Information Disclosure Statement

The information disclosure statement filed on April 27, 2005 and December 9, 2005 for which a copy of the patent publication has been submitted in this application has been considered as shown by the Examiners signature next to each reference.

Oath/Declaration

The oath or declaration submitted on January 9, 2006 has been reviewed and is in compliance with 37 CFR 1.56.

Specification

The abstract of the disclosure is objected to because of improper English. For example on line 3-4 the abstract recites "...(a) a mutant tyrosyl-tRNA synthetase that is a mutation of tyrosyl-tRNA synthetase...". It is suggested in this case to amend this term by "...a mutant tyrosyl-tRNA synthetase that is derived from of tyrosyl-tRNA synthetase..." Correction throughout the abstract is required. See MPEP § 608.01(b).

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 20 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "Method of Expressing Proteins comprising non-naturally-occurring amino acids".

The specification fails to comply 37 CFR 1.821-1-825 that require for each sequence present in the specification to be assigned a sequence identifier. In the instant case, the requirements are not met because there are two nucleotide sequences (representing tRNA molecules in figure 2) and a polypeptide sequence (comprising 424 amino acids in figure 8) that are not assigned SEQ ID NOs. Appropriate correction is required.

Claim Objections

Claim 1 is objected to because the pre-amble recites: "...for non-naturally-occurring protein..." which is improper English. It is suggested that applicants amend the claim to recite: "...for non-naturally-occurring proteins..."

Claim 7 is objected to because of the following informalities: Reference to "...any of the methods according to claim 1 " is improper referring only to claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is rejected because of the recitation "...position 37... at position 195 ..." without specifying the sequence of the mutant tyrosyl tRNA synthetase derivative from the specific E. coli strain.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The court of appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as structure, formula [or] chemical name, 'of the claimed subject matter sufficient to distinguish it from other material. " For claims drawn

to a genus, MPEP § 2163 states the written description required for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by a disclosure of relevant identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses the structure of only some representative species of such mutant tyrosyl-tRNA synthetases (page 14, table 1). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a mutant tyrosyl-tRNA synthetase. In addition the specification fails to describe any other tyrosine derivative other than a 3-substituted or a 4-substituted tyrosine derivatives in the expression method to produce a protein with non-naturally occurring amino acids.

Furthermore claims 1-7 are drawn to a genus of suppressor tRNA molecules described only by function and fails to describe any suppressor tRNA by any structure. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case the recited genus of mutant tyrosyl-tRNA synthetase, tRNA molecules and the tyrosine

derivatives encompass species widely variant with respect to their structures. Thus functional description of a mutant tyrosyl-tRNA synthetase, a suppressor tRNA and two tyrosine derivatives of tyrosine derivatives do not provide adequate written description. Mutant tyrosyl-tRNA synthetase and/or tRNA molecules may have any combination of alterations, including any addition, substitution, deletion and/or insertion in addition to the positions described in claim 4 and 5, tyrosine derivatives may also carry a wide variety of substituents. As such, the disclosure of the single mutant tyrosyl-tRNA synthetases, a suppressor tRNA and two tyrosine derivatives described in claim 1-7 as broadly interpreted are insufficient to be representative of the attributes and features of all species encompassed by the claimed genus of tyrosyl-tRNA synthetases to be used in the method.

Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a specific mutant tyrosyl-tRNA synthetase comprising V37C195 and a specific mutant tRNA derived from *Bacillus searothermophilus* in the method of producing a protein comprising the 3-substituted tyrosine unnatural amino acid in an isolated animal cell, does not reasonably provide enablement for a method that uses any mutant tyrosyl-tRNA synthetase comprising any

number of mutations at any position to produce a protein with any unnatural amino acid(s) or with any 4-substituted tyrosine residue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988). The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass using any tyrosyl tRNA synthetase mutant that can be expressed in an animal cell in view of producing a protein comprising an unnatural amino acid(s). The specification provides guidance and examples for making specific mutant tyrosyl tRNA synthetase molecules such as the V37C195 mutant that can function in an isolated animal cell in the presence of a chimeric tRNA comprising a partial sequence from *Bacillus stearothermophilus* and a human tRNA gene (specification page 28) to produce a protein comprising the unnatural amino acid 3-iodotyrosine. However, the specification does not teach the specific structure of any other mutant tyrosyl tRNA synthetase as broadly encompassed by the claims and use of the same in a method of producing a protein comprising any

unnatural amino acid as encompassed by claims 1, 3-7 or any 4-substituted tyrosine as encompassed in claim 2.

The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed invention is enormous and undue. Such experimentation entails performing any genetic mutation on any mutant tyrosyl tRNA synthetase derived from E. coli and using said mutant synthetase to incorporate any unnatural amino acid (claims 1, 3-7) or any 3 or 4-substituted tyrosine (claim 2) into a protein.

Thus, searching for the specific mutant tyrosyl tRNA synthetase and a corresponding tRNA that can be used in a method of incorporating any unnatural amino acid or any 3 or 4-substituted unnatural amino acid in a protein is well outside the realm of routine experimentation because the specification does not enable how or what structural features in the tyrosyl-tRNA synthetase derived from E. coli need to be mutated and/or must be conserved to allow said synthetase to aminoacylate any tRNA (derived from Bacillus stearothermophilus) with any unnatural amino acid or with 3 or 4 substituted tyrosine residue.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific mutations of the tyrosyl tRNA synthetase derived from E. coli, the specific tRNA that function to incorporate a specific unnatural amino acid or a group of unnatural amino acids that can be aminoacylated onto a

corresponding mutant tRNA. Without such guidance, the experimentation left to those skilled in the art is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Sakamoto et al. (Site-specific incorporation of an unnatural amino acid into proteins in mammalian cells, Nucleic Acids Research. Nov. 01, 2002. Vol.30, No. 21; pg. 4692).

Sakamoto et al disclose a method of incorporating unnatural amino acids into proteins in mammalian cells. More particularly Sakamoto et al disclose a method wherein an *E. coli* tyrosyl-tRNA synthetase mutant, V37C195, a suppressor tRNA derived from *Bacillus stearothermophilus,* a nucleic acid comprising an amber codon in the coding region tyrosine into proteins were used to incorporate the unnatural amino acid 3-iodo-L-tyrosine at a desired position in mammalian cells (CHO-Y cells). Therefore Sakamoto et al's disclosure anticipates claims 1-7 in the instant Application.

Claims 1-3, 6-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Schultz et al (Application 10/126,931 now US PAT 7083970). Schultz et al teach a method wherein site-selective incorporation of one or more unnatural amino acids including 3-substituted tyrosine and 4-iodo-substituted tyrosine into proteins in vivo (fig. 31, see S56 and S57). Schultz et al further teach that their method can be used in both prokaryotic and eukaryotic cells. For this purpose, Schultz et al teach the use of specific vectors to introduce the nucleic acid target that comprises generic expression cassettes containing at least one independent terminator sequence, sequences permitting replication of the cassette in eukaryotes, or prokaryotes, or both, (e.g., shuttle vectors) and selection markers for both prokaryotic and eukaryotic systems.

The instant claims recite derivatives of specific tyrosyl-tRNA synthetases and tRNA molecules to be used to incorporate unnatural amino acids or 3-substituted iodo-tyrosine or 4-substituted iodo-tyrosine into a protein of interest in animal cells. Therefore the disclosure by Schultz et al anticipates all the limitations in claims 1-3, 6-7 in the instant Application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kiga et al (An Engineered Escherichia coli tyrosyl-tRNA synthetase for Site Specific incorporation of an unnatural amino acid into proteins in Eukaryotic translation and its application in wheat germ cell-free systems. PNAS July 23, 2002).

Kiga et al teach tyrosyl tRNA from Escherichia coli (E. Coli) was engineered to preferentially recognize 3-iodo-L-tyrosine rather than L-tyrosine for the site-specific incorporation of 3-iodo-L-tyrosine into proteins in eukaryotic translation systems. They further teach that they engineered the mutant E. coli tyrosyl-tRNA synthetase based on the three dimensional crystal structure of *Bacillus stearothermophilus* TyrRS. A specific E. coli tyrosyl-tRNA synthetase mutant comprising change at positions Y37Q195 to V37C195 was found to preferentially incorporate 3-iodo-L-tyrosine rather than L-tyrosine into a protein of interest. Kiga et al teach the use of their Eukaryotic translation system is advantageous for incorporating unnatural amino acids into eukaryotic proteins, because some eukaryotic proteins are not properly folded to their native conformation in prokaryotic systems, which provides a motivation to one of ordinary skill in the art to use a Eukaryotic system for Eukaryotic proteins of interest.

Furthermore Kiga et al suggest that the use of their translation system must be expanded to include mammalian cells (page 9720, second column, last paragraph). Therefore both the motivation and the suggestion for the use of animal cell to produce eukaryotic proteins of interest are found in Kiga et al's teachings.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5: 30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Examiner: Kagnew Gebreyesus PhD.
Feb. 16, 2007.
KG

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER